1,003,950

PATENT SPECIFICATION

NO DRAWINGS

1,003,950

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Int. Cl.:—C 07 c, d // C 07 f

COMPLETE SPECIFICATION

Process for the Production of Basic Dibenzo-Oxepin and Dibenzo-Thiepin Derivatives

We, C. F. BOEHRINGER & SOEHNE G.m.b.H., a body corporate organised under the laws of Germany, of Mannheim-Waldhof, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

PATENTS ACT, 1949

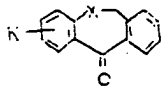
SPECIFICATION NO. 1,003,950

Reference has been directed, in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to Patent No. 1,001,822, 1,001,824 and 1,001,825

THE PATENT OFFICE,
10th May, 1965

D 70693/9

in which X is an oxygen or sulphur atom, R is a hydrogen or halogen atom or an alkyl or alkoxy radical and A is a tertiary amino group and the acid addition salts and quaternary ammonium compounds thereof, these compounds being produced when a cyclic ketone of the general formula:—

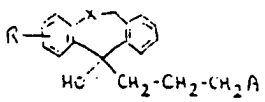


(II)

in which R and X have the above-given meanings, is reacted with a Grignard compound of the general formula

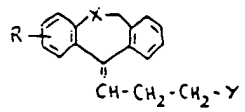
$$Hal—Mg—CH_2—CH_2—CH_2—A,$$

in which A has the above-given meaning and Hal is a halogen atom, and the addition product so obtained decomposed, to give a carbinol of the general formula:—



in which A, R and X have the above-given meanings, and water split off from this carbinol to give the desired compound, which is, if desired, converted into an acid addition salt or a quaternary ammonium compound. The preferred tertiary amino groups A are, for example, dialkylamino groups or nitrogen-containing heterocyclic radicals, such as piperidino, pyrrolidino, morpholino or piperazino residues, which may also be substituted.

We have now found that compounds of general formula (I) can also be produced by reacting compounds of the general formula: —



(III)

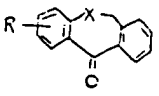
in which X and R have the same meanings as above and Y represents a halogen atom or a sulphonic acid ester group of the general formula —O—SO_2—R_1, in which R_1 is an alkyl or aryl radical, with compounds of the general formula H—A, in which A has the above-given meaning.

The reaction is carried out by boiling the two reaction components at atmospheric or increased pressure in a suitable solvent, preferably ethanol/tetrahydrofuran. After the usual working up and purification, the bases obtained of general formula (I) can, if desired, be converted into their salts in known manner.

The advantage of the process according to the present invention, in comparison with the process of the Parent Specification, lies in that, from the same starting material (III), there can be obtained compounds of general formula (I) with various basic residues, whereby A can be not only a simple unsubstituted tertiary amino group but can also be derived from compounds which carry reactive substituents, such as 4 - (β - hydroxyethyl) - piperidine or N¹ - (β - hydroxyethyl) - piperazine residues.

The compounds of general formula (III) required as starting materials are new and can be produced in various ways:

Ketones of general formula

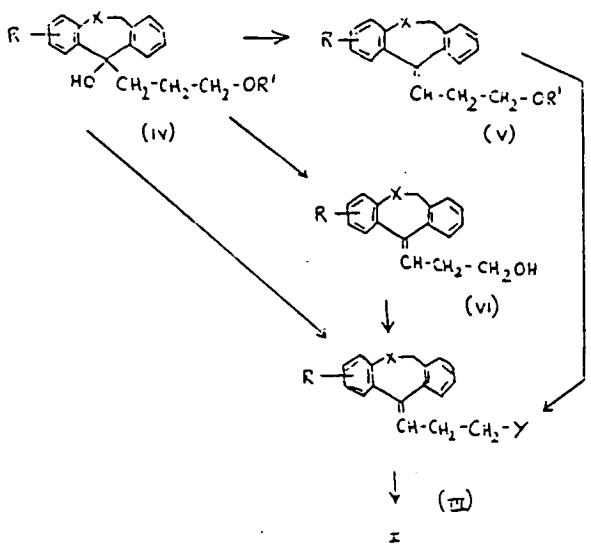


(II)

in which R and X have the same meanings as above, are reacted with Grignard compounds of the general formula

$$Hal—CH_2—CH_2—CH_2—OR^1,$$

in which Hal is a halogen atom and R^1 is a methyl, *tert.*-butyl or benzyl radical, to give compounds of general formula (IV) and these carbinols (IV) are converted directly, for example, by treatment with boiling aqueous hydrobromic acid, into compounds of general formula (III) in which Y is a bromine atom. The starting compounds of general formula (III) can also be obtained when there are first produced from the carbinols (IV) in which R^1 is a methyl or benzyl radical, the alkylidene derivatives of general formula (V) by boiling with acetyl chloride in benzene or alcoholic hydrochloric acid and these converted into compounds of general formula (III) in which Y is a bromine atom with boiling hydrobromic acid. Carbinols of general formula (IV) in which R^1 is a *tert.*-butyl radical, give, upon boiling with alcoholic hydrochloric acid, compounds of general formula (VI) which can be converted with, for example, thionyl chloride, into compounds of general formula III in which Y is a chlorine atom. The reactions involved are illustrated in the following reaction sequence: —



The following Examples are given for the purpose of illustrating the present invention, the percentages being by weight:—

EXAMPLE 1:

11 - (3 - dimethylamino - propylidene) - 6,11 - dihydro - dibenzo - [b,e] - thiepin.

METHOD I:

(a) A Grignard compound is produced from 48 ml. 1 - benzyloxy - 3 - chloropropane obtained according to the method of Bennett and Hock, J.C.S., *1927*, pp. 473, 476) and 6.3 g. magnesium in 100 ml. ether, in the presence of 1 ml. methyl iodide, by boiling for about 2 hours until all the magnesium has reacted. Subsequently, 38.8 g. 6,11 - dihydro - dibenzo - [b,e] - thiepin - 11 - one, dissolved in 70 ml. of a mixture of tetrahydrofuran/ether (1:1), is added dropwise at room temperature, whereby the reaction mixture slowly begins to boil. The reaction mixture is boiled for 4 hours, cooled, an ammonium chloride solution added and the mixture extracted with ether. The combined and dried solvent extracts are freed from solvent and the oily residue (75.8 g.) is crystallised by trituration with 115 ml. ligroin/ether (9:1). There are thus obtained 43.5 g. (68.5% of theory) 11 - (3 - benzyloxypropyl) - 11 - hydroxy - 6,11 dihydrodibenzo - [b,e] - thiepin with a melting point of 69—73°C. By recrystallisation from isopropanol, the melting point rises to 76—77°C.

(b) 10 g. 11 - (3 - benzyloxypropyl) - 11 - hydroxy - 6,11 - dihydro - dibenzo - [b,e] - thiepin, obtained according to (a), and 20 ml. acetyl chloride are boiled for 1 hour in 100 ml. chloroform. Volatile material is removed in a vacuum on a water bath and the residue distilled in a high vacuum. Yield: 8.4 g. (88.5% of theory) 11 - (3 - benzyloxypropylidene) - 6,11 - dihydro - dibenzo - [b,e] - thiepin with a boiling point of 245—250°C./0.1 mm Hg.

(c) 16.5 g. 11 - (3 - benzyloxypropylidene) - 6,11 - dihydrodibenzo - [b,e] - thiepin, obtained according to (b), are boiled, with stirring, for 3 hours with 100 ml. 48% hydrobromic acid. At the end of the reaction, the reaction mixture is diluted with water, extracted with ether and the combined ether extracts washed neutral, dried and the solvent removed. The crude product obtained (18.3 g.) is brought to crystallisation with a mixture of ligroin and ether. There are thus obtained 6.6 g. (43.5% of theory) 11 - (3 - bromopropylidene) - 6,11 - dihydrodibenzo - [b,e] - thiepin with a melting point of 132—136°C. By recrystallisation from cyclohexane, the melting point rises to 142—143°C.

(d) 3.3 g. (0.01 mol) 11 - (3 - bromopropylidene) - 6,11 - dihydro - dibenzo - [b,e] - thiepin, obtained according to (c), are dissolved in 15 ml. tetrahydrofuran and heated at 95—100°C (boiling water bath) for 3 hours in a glass autoclave, together with a solution of 2.7 g. (0.06 mol) dimethylamine in 10 ml. ethanol. Water and 6N hydrochloric acid are added and the reaction mixture is extracted with

ether. The separated, aqueous acid part is rendered alkaline with a dilute sodium hydroxide solution and the oil which separates is taken up in ether. The ethereal solution is dried and the ether distilled off, leaving a residue, which, upon high vacuum distillation, yields 1.8 g. (61% of theory) 11 - (3 - dimethylamino - propylidene) - 6,11 - dihydrodibenzo - [b,e] - thiepin with a boiling point of 176—178°C./0.1 mm Hg; the hydrochloride melts at 218—220°C. (recrystallised from isopropanol).

Simplified method II:

22.6 g. (0.1 mol) 6,11 - dihydro - dibenzo - [b,e] - thiepin - 11 - one are dissolved in 20 ml. tetrahydrofuran and 20 ml. ether and reacted, as described above under (a), with 3.6 g. (0.16 gram atoms) magnesium and 28 g. (0.2 mol) 1 - benzyloxy - 3 - chloropropane in 60 ml. ether. After decomposition with an ammonium chloride solution, there are obtained 51.1 g. crude 11 - (3 - benzyloxypropyl) - 11 - hydroxy - 6,11 - dihydro - dibenzo - [b,e] - thiepin which is boiled for 1 hour with 200 ml. approximately 3N alcoholic hydrochloric acid. After evaporation of the solvent, there are obtained, by high vacuum distillation, 29.2 g. 11 - (3 - benzyloxypropylidene) - 6,11 - dihydro - dibenzo - [b,e] - thiepin; yield: 81.5% (referred to the thiepinone derivative used).

13.5 g. of this benzyloxypropylidene compound and 80 ml. 48% hydrobromic acid are boiled for 3 hours and worked up as described above under (c). The so obtained crude bromopropylidene compound (15 g.) is taken up in 37 ml. tetrahydrofuran and reacted, as described above under (d), with 9.8 g. dimethylamine in 37 ml. absolute ethanol. After a high vacuum distillation, there are obtained 4.3 g. 11 - (3 - dimethylamino - propylidene) - 6,11 - dihydro - dibenzo - [b,e] - thiepin with a boiling point of 168—175°C./0.1 mm. Hg; the hydrochloride melts at 216—218°C. (recrystallised from isopropanol). Yield: 38.5%, referred to the benzyloxy - propylidene compound, or 31.5%, referred to the initially used thiepinone derivative.

Example 2.

11 - (3 - monomethylamino - propylidene) - 6,11 - dihydro - dibenzo - [b,e] - thiepin.

3.3 g. (0.01 mol) 11 - (3 - bromopropylidene) - 6,11 - dihydro - dibenzo - [b,e] - thiepin are dissolved in 15 ml. tetrahydrofuran and heated, together with a solution of 2 g. (0.06 mol) monomethylamine in 10 ml. ethanol, for 3 hours at 90 — 100°C. After working up analogously to Example 1 (d), there are obtained 1.4 g. (50% of theory) 11 - (3 - monomethylamino - propylidene) - 6,11 - dihydro - dibenzo - [b,e] - thiepin with a boiling point of 183—187°C./0.1 mm Hg; the hydrochloride melts at 235—237°C. (recrystallised from isopropanol).

Example 3.

11 - {3 - [4 - (2 - hydroxyethyl) - piperidyl] - propylidene} - 6,11 - dihydro - dibenzo - [b,e] - thiepin.

16.5 g. (0.05 mol) 11 - (3 - bromopropylidene) - 6,11 - dihydro - dibenzo - [b,e] - thiepin are dissolved in 75 ml. tetrahydrofuran and boiled for 5 hours, together with 20 g. (0.15 mol) 4 - (2 - hydroxyethyl) - piperidine (prepared according to the method of K. Stach *et al.*, Monatsh., *93*, 1090/1962).

After the addition of dilute hydrochloric acid and ether, the aqueous acid part is separated off, rendered alkaline with a dilute sodium hydroxide solution and extracted with ether. The ethereal solution is dried and the ether distilled off, leaving a residue which, upon high vacuum distillation, yields 11.9 g. (65.6% of theory) 11 - {3 - [4 - (2 - hydroxyethyl) - piperidyl] - propylidene} - 6,11 - dihydro - dibenzo - [b,e] - thiepin with a boiling point of 235—255°C./0.01 mm Hg; m.p. 50—52°C.

Example 4.

11 - {3 - [4 - (2 - hydroxyethyl) - piperazinyl - (1)] - propylidene} - 6,11 - dihydro - dibenzo - [b,e] - thiepin.

6 g. (0.018 mol) 11 - (3 - bromopropylidene) - 6,11 - dihydro - dibenzo - [b,e] - thiepin are dissolved in 30 ml. tetrahydrofuran and boiled for 5 hours with 4.7 g. (0.036 mol) 4 - (2 - hydroxyethyl) - piperazine (prepared according to the method of S. McElvain *et al.*, J.A.C.S., *76*, 1126/1954). Working up is carried out as described in Example 3 and there are obtained 4.0 g. (44% of

6,11 - dihydro - dibenzo - [b,e] - oxepin with a boiling point of 158—165°C./0.01 mm Hg; m.p. 60—62°C.

EXAMPLE 7.

11 - {3 - [4 - (2 - hydroxyethyl) - piperazinyl - (1)] - propylidene} - 6,11 - dihydro - dibenzo - [b,e] - oxepin.

6.5 g. of the methane - sulphonic acid ester of 11 - (3 - hydroxypropylidene) - 6,11 - dihydro - dibenzo - [b,e] - oxepin and 6 g. N - β - hydroxyethyl - piperazine are dissolved in 30 ml. absolute tetrahydrofuran and boiled for 2 hours. After the addition of water and ether, the ethereal part is separated off and extracted several times with water and subsequently with dilute hydrochloric acid. The aqueous acid solution is now rendered alkaline with a sodium hydroxide solution and extracted with ether. The ether extract is dried and evaporated to dryness and the residue again taken up in absolute ether; the corresponding hydrochloride is precipitated with ethereal hydrochloric acid and, after filtration, boiled with dioxan for a short time. There are thus obtained 4.3 g. of the dihydrochloride of 11 - {3 - [4 - (2 - hydroxyethyl) - piperazinyl - (1)] - propylidene} - 6,11 - dihydro - dibenzo - [b,e] - oxepin (43% of theory) with a melting point of 231—232°C. The compound crystallises with 0.25 mol water of crystallisation.

The methane - sulphonic acid ester of 11 - (3 - hydroxypropylidene) - 6,11 - dihydro - dibenzo - [b,e] - oxepin used as starting material is prepared as follows: 7.0 g. 11 - (3 - hydroxypropylidene) - 6,11 - dihydro - dibenzo - [b,e] - oxepin are dissolved in 45 ml. pyridine and cooled to 0°C. 5.8 g. methane - sulphonic acid chloride are now added dropwise at 0—3°C., with stirring, the reaction mixture is stirred for 30 minutes at 0°C. and subsequently for 1 hour at 20°C. The reaction product is poured on to ice, mixed with water and ether and the ethereal part treated with dilute aqueous hydrochloric acid and subsequently with water. After drying the ethereal part with anhydrous sodium sulphate, the solvent is evaporated to a small volume, whereby a crystalline slurry separates. There are obtained 6.6 g. of the ester (71.7% of theory) with a melting point of 105—107°C.

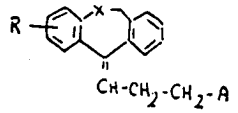
EXAMPLE 8.

11 - {3 - [4 - (2 - hydroxyethyl) - piperidyl] - propylidene} - 6,11 - dihydro - dibenzo - [b,e] - oxepin.

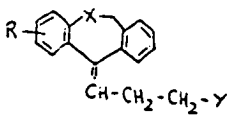
In a manner analogous to that described in Example 7, there are obtained from 6.0 of the methane - sulphonic acid ester of 11 - (3 - hydroxypropylidene) - 6,11 - dihydro - dibenzo - [b,e] - oxepin and 5.6 g. 4 - (2 - hydroxyethyl) - piperidine, 6.7 g. crude 11 - {3 - [4 - (2 - hydroxyethyl) - piperidyl] - propylidene} - 6,11 - dihydro - dibenzo - [b,e] - oxepin (88% of theory). From a solution of this compound in absolute ether, there can be precipitated, with ethereal hydrochloric acid, the corresponding hydrochloride which, after recrystallisation from a mixture of isopropanol - ethyl acetate (1:1), melts at 193—195°C. Yield: 6.5 g. (79% of theory); the compound crystallises with 0.25 mol water of crystallisation.

WHAT WE CLAIM IS:—

1. Process for the production of basic dibenzo - [b,e] - oxepin and -thiepin derivatives of the general formula:—



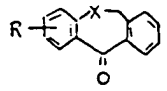
in which X is an oxygen or sulphur atom, R is a hydrogen or halogen atom or an alkyl or alkoxy radical and A is a tertiary amino group, and their acid addition salts, wherein a dibenzo - [b,e] - oxepin or -thiepin of the general formula:—



in which X and R have the same meanings as above and Y represents a halogen atom or a sulphonic acid ester group of the general formula —O—SO_2—R_1, in which R_1 is an alkyl or aryl radical, is reacted with a compound of the general formula

H—A, in which A has the above-given meaning, and the compound obtained is, if desired, converted into an acid addition salt.

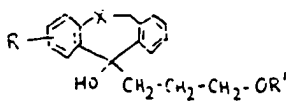
2. Process according to claim 1, wherein the dibenzo - oxepin or -thiepin used as starting material is obtained by reacting a ketone of the general formula:—



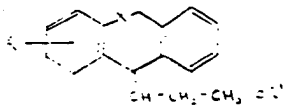
in which R and X have the same meanings as above, with a Grignard compound of the general formula:—

$$Hal—CH_2—CH_2—CH_2—OR^1$$

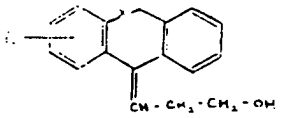
in which Hal is a halogen atom and R^1 is a methyl, *tert.* - butyl or benzyl radical to give a carbinol of the general formula:—



in which R^1, R and X have the same meanings as above and this carbinol is (a), in the case in which R^1 is a methyl, *tert.* - butyl or benzyl radical, reacted with boiling aqueous hydrobromic acid to give a dibenzo - oxepin or -thiepin compound in which Y is a bromine atom, or (b), in the case in which R^1 is a methyl or benzyl radical, boiled with acetyl chloride in benzene or with alcoholic hydrochloric acid to give an alkylidene derivative of the general formula:—



in which R, R^1 and X have the same meanings as above, which is, in turn, reacted with boiling hydrobromic acid to give a dibenzo - oxepin or -thiepin compound in which Y is a bromine atom, or (c), in the case in which R^1 is a *tert.* - butyl radical, boiled with alcoholic hydrochloric acid to give a compound of the general formula:—



in which R and X have the same meaning as above, which is then reacted with thionyl chloride to give a dibenzo - oxepin or -thiepin compound in which Y is a chlorine atom.

3. Process according to claim 1 for the production of basic dibenzo - [b,e] - oxepin and -thiepin derivatives, substantially as hereinbefore described and exemplified.

4. Basic dibenzo - [b,e] - oxepin and -thiepin derivatives, whenever prepared by the process according to any of claims 1 to 3.

5. 11 - {3 - [4 - (2 - hydroxyethyl) - piperidyl] - propylidene} - 6,11 - dihydro - dibenzo - [b,e] - thiepin.

6. 11 - {3 - [4 - (2 - hydroxyethyl) - piperazinyl - (1)] - propylidene} - 6,11 - dihydro - dibenzo - [b,e] - thiepin.

7. 11 - {3 - [4 - (2 - hydroxyethyl) - piperazinyl - (1)] - propylidene} - 6,11 - dihydro - dibenzo - [b,e] - oxepin.

S. 11 - {3 - [4 - (2 - hydroxyethyl) - piperidyl] - propylidene} - 6,11 - dihydro - dibenzo - [b,e] - oxepin.

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